Armed Forces College of Medicine

AFCM

Viral Encephalitis

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INTENDED LEARNING OBJECTIVES (ILO)

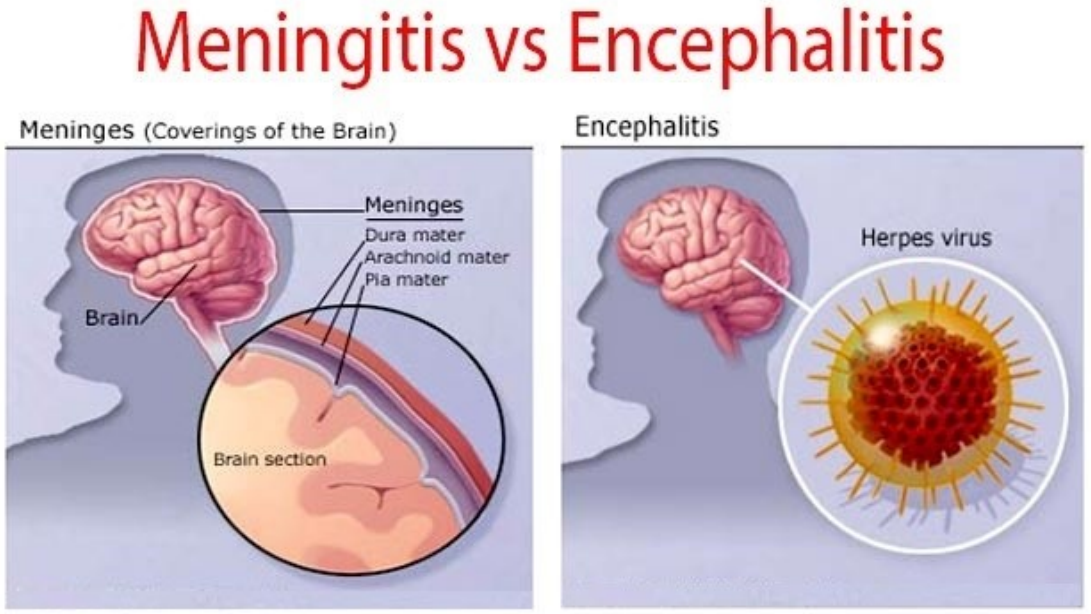
By the end of this lecture the student will

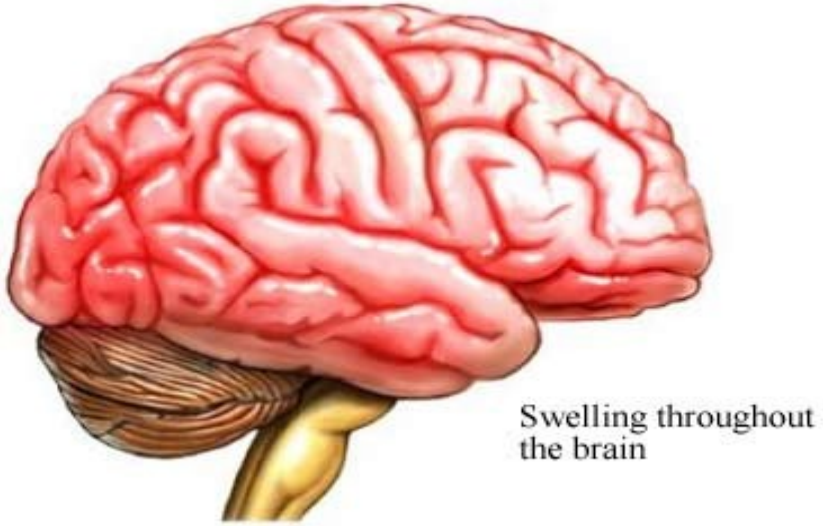
be able to:

1. Describe pathogenesis & clinical manifestations of viral encephalitis.
2. Outline the laboratory diagnosis of viral encephalitis.
3. Outline prevention and control of viral encephalitis .

Encephalitis & Meningoencephaliti

- ✓ **Encephalitis** is an infection of **the brain parenchyma**, most commonly caused by **VIRUSES**.
- ✓ **Meningoencephalitis** is an infection **of both** the brain and the

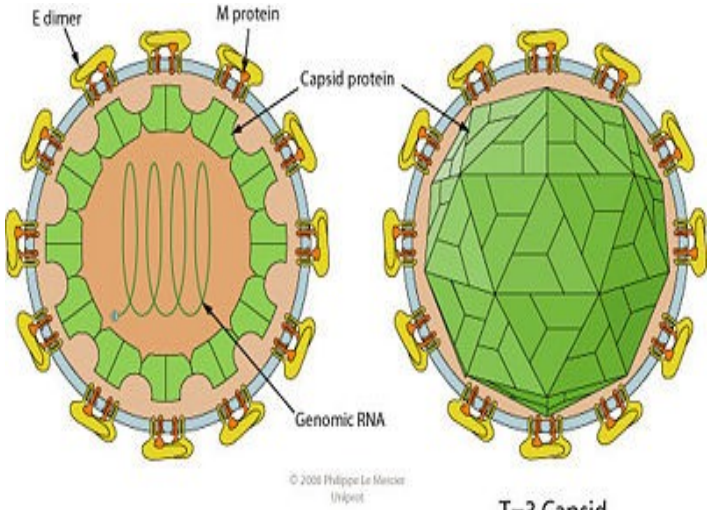




Encephalitis by Arboviruses

West Nile Virus

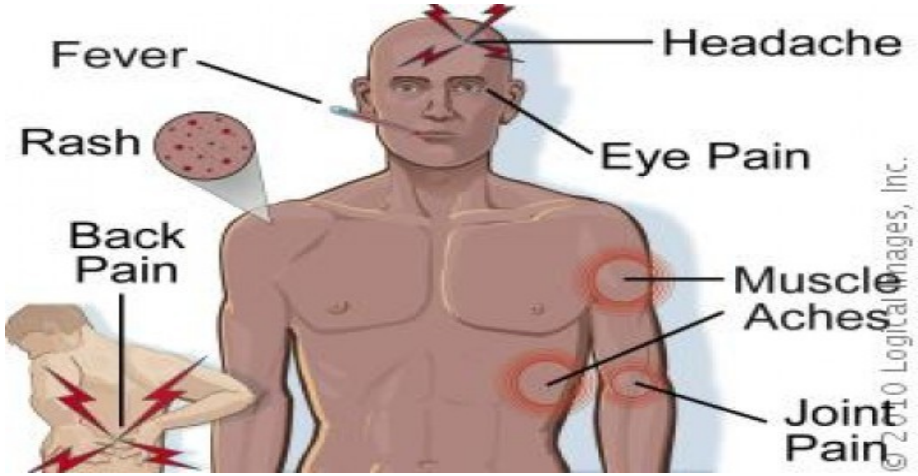
Structure	A-Family : Flavivirus : B Nucleocapsid : 1- ssRNA 2- Icosahedral C-Enveloped
Pathogen.	
A-Transmission	Endemic in Africa & USA **(commonest arboviral cause)**
1-Reservoir	**Wild birds e.g crows , jays**
2-Vector	**Culex** mosquitoes
3-Mode	**Bite of mosquito** ■ **Humans are dead end host → No human to human transmission?** **Viremia is too low & too brief** for the next bite to

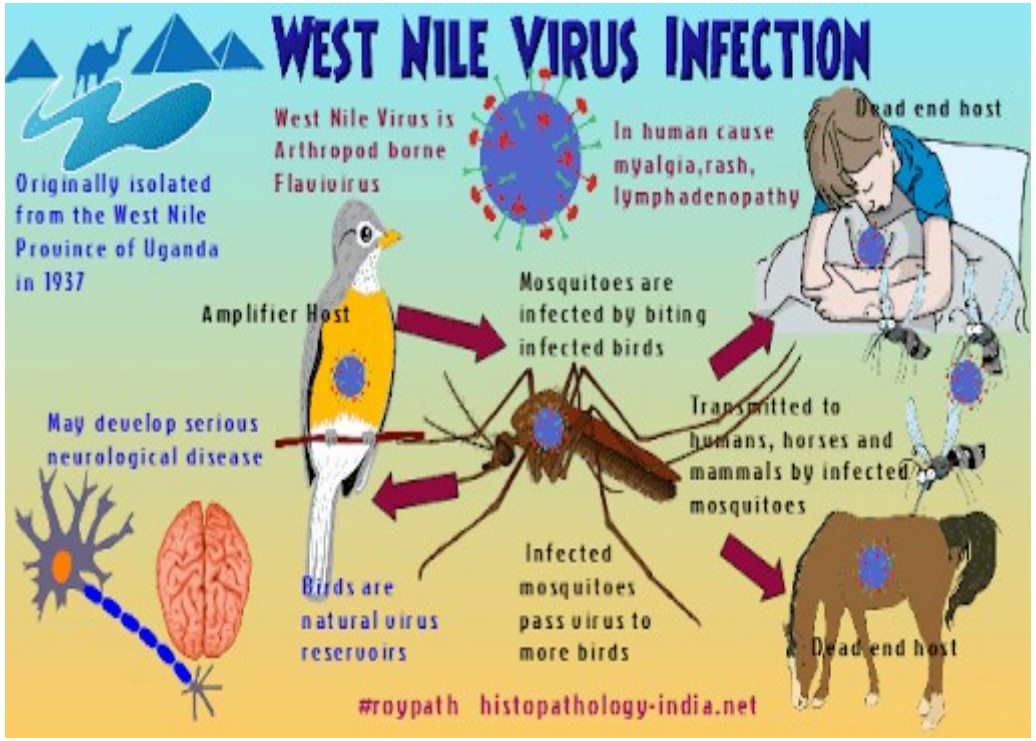


Mosquitoes can pass the virus to humans, horses, and other mammals.
West Nile virus Cycles between mosquitoes and birds.
WEST NILE V
The 4 D's
1. DRAIN standing w
2. Stay inside at DA
3. DRESS appropriat
4. Use DEET
For More info
www.FightTheBite

Encephalitis by Arboviruses

Clinical manifest.	**1-Asymptomatic : 80%** of infections 2-Fever and headache without encephalitis : 20% **3-Encephalitis** with or without signs of meningitis : **only 1% (mainly in persons > 60 years)**
Lab. diag.	
1-RT-PCR	Detection of **RNA in spinal fluid &blood**
2-Serology	**IgM** in spinal fluid
3-Isolation	From brain tissue
Prevention	**1. No vaccine**




WEST NILE VIRUS INFECTION
Originally isolated from the West Nile Province of Uganda in 1937
West Nile Virus is Arthropod borne Flavivirus
In human cause myalgia,rash, lymphadenopathy
Dead end host
Amplifier Host
Mosquitoes are infected by biting infected birds
May develop serious neurological disease
Transmitted to humans, horses and mammals by infected mosquitoes
Birds are natural virus reservoirs
Infected mosquitoes pass virus to more birds
Dead end host
#roypath histopathology-india.net

Rabies virus

Infects all mammals

Neurotropic virus

Lethal acute encephalitis

Rabies virus

Structure

A-Family : Rhabdovirus

B-Nucleocapsid

1-ssRNA

2-Helical

3- Bullet shaped

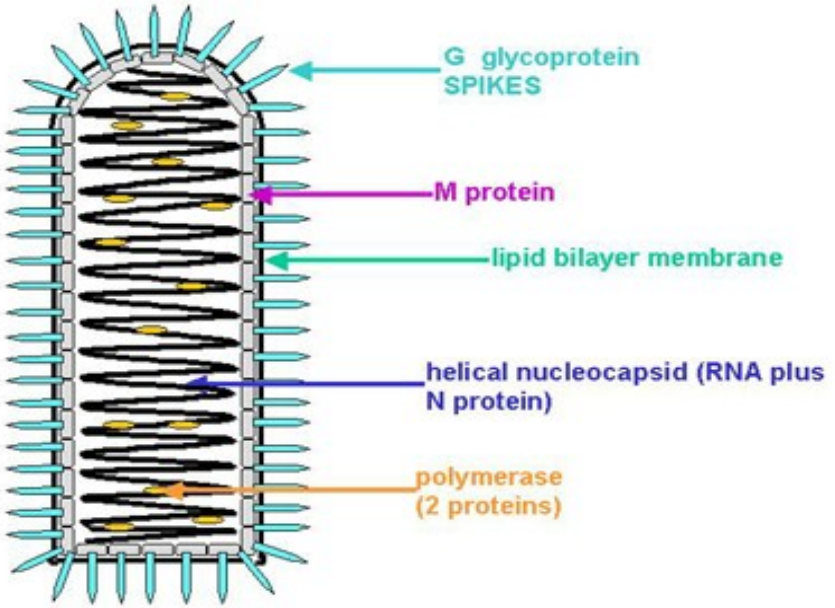
C-Enveloped,

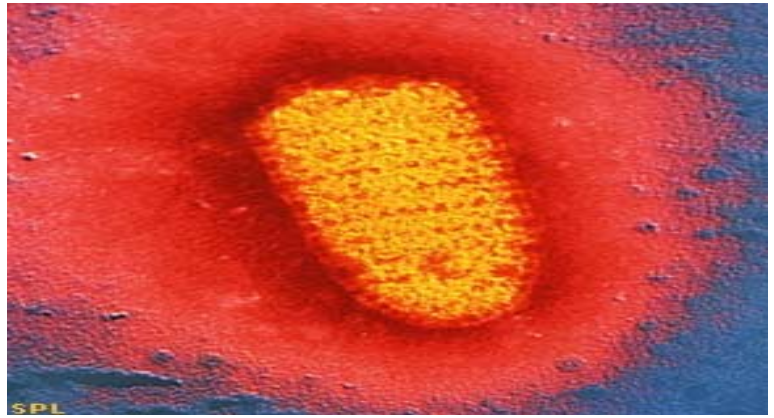
with **glycoprotein projections :**

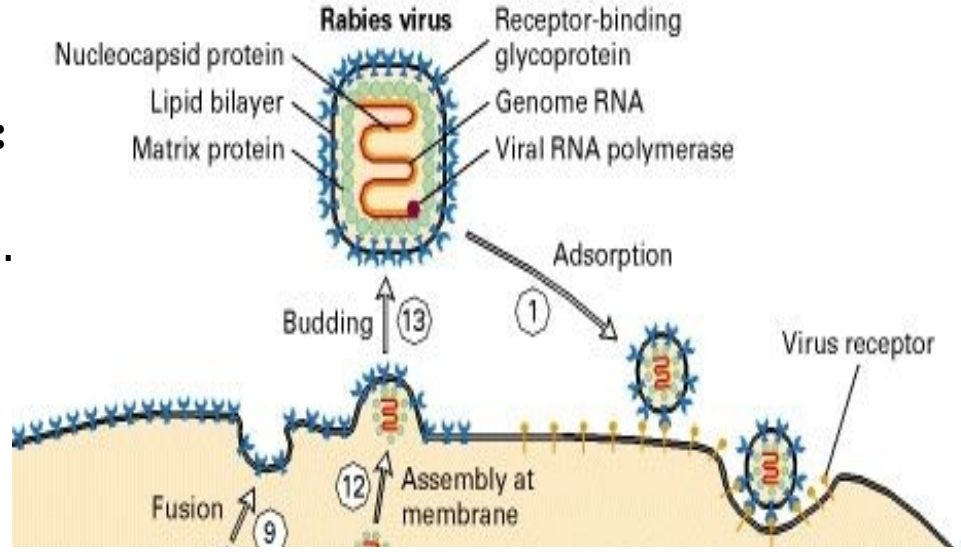
a-Antigen (**single** antigenic type.

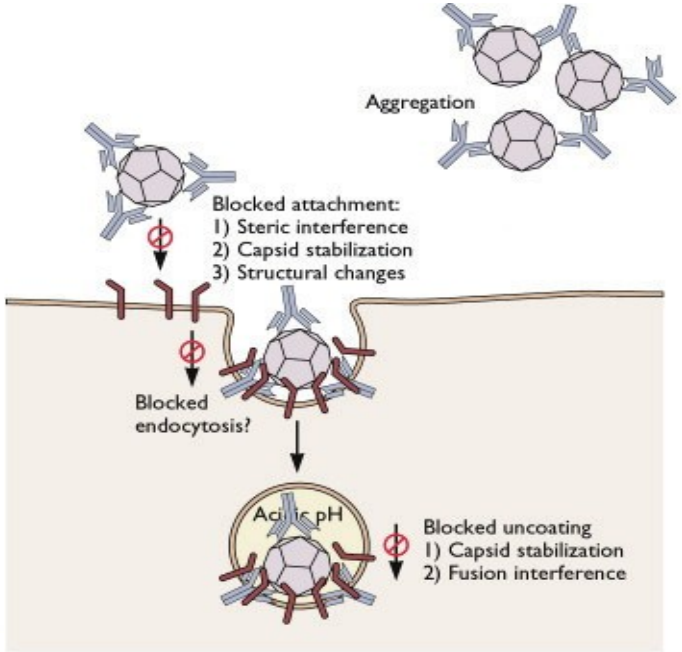
b-Viral attachment

Target of **neutralizing** Abs









Rabies virus

Pathogenesis

A-Animal reservoirs

- **Dogs & cats**
- Wild carnivores e.g. foxes and wolves
- **Bats**

B-Modes of transmission

1-The bite or scratch by a rabid animal

Rabies virus is present in saliva of rabid animal **e.g Dogs (main source)**

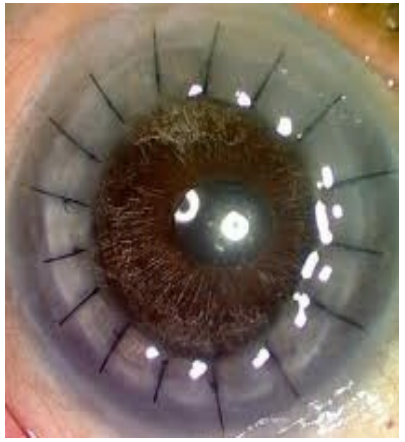
Manifest aggressive, biting behavior induced by the viral encephalitis

2-Non-bite exposures

1-Exposure to aerosols of **bat secretions (healthy)**& in laboratory

2- Corneal transplantation (very rare) **:**

from infected humans who died from undiagnosed rabies**.**



C- Site of replication

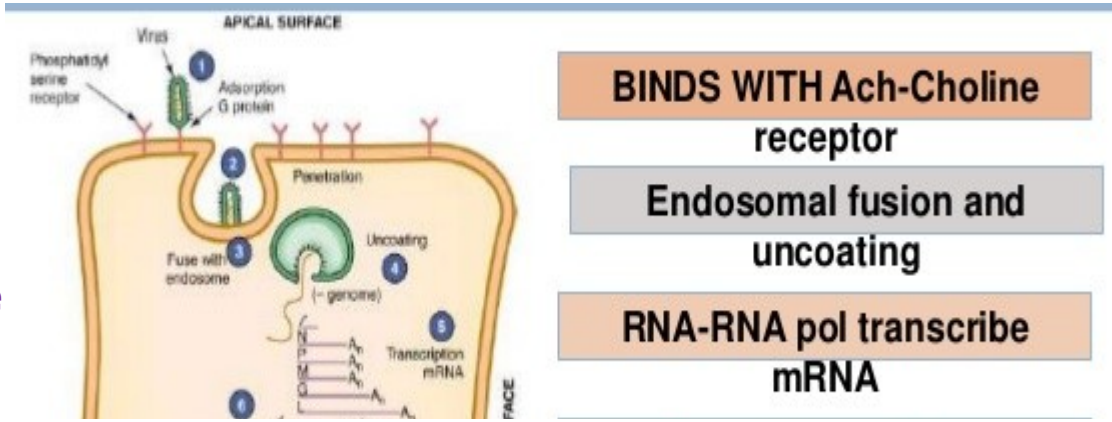
The virus replicates in **striated muscles** at the site of bite

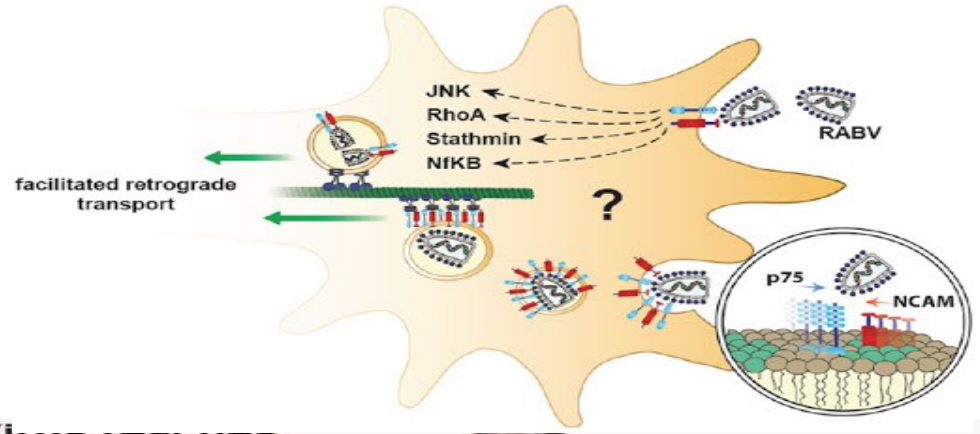
→ Infects the sensory neurons by attaching to **acetylcholine rece**

→ **Retrograde axonal transport**

→ Move along the **peripheral nerves to the spinal cord & brain**

→ Multiplication





D-Effect on nerve cells

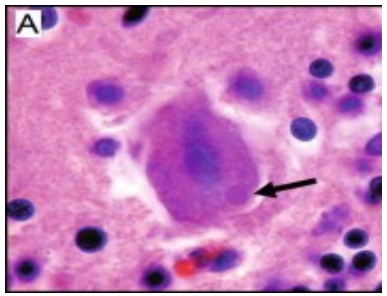
Encephalitis **Demyelination** **Negri bod**

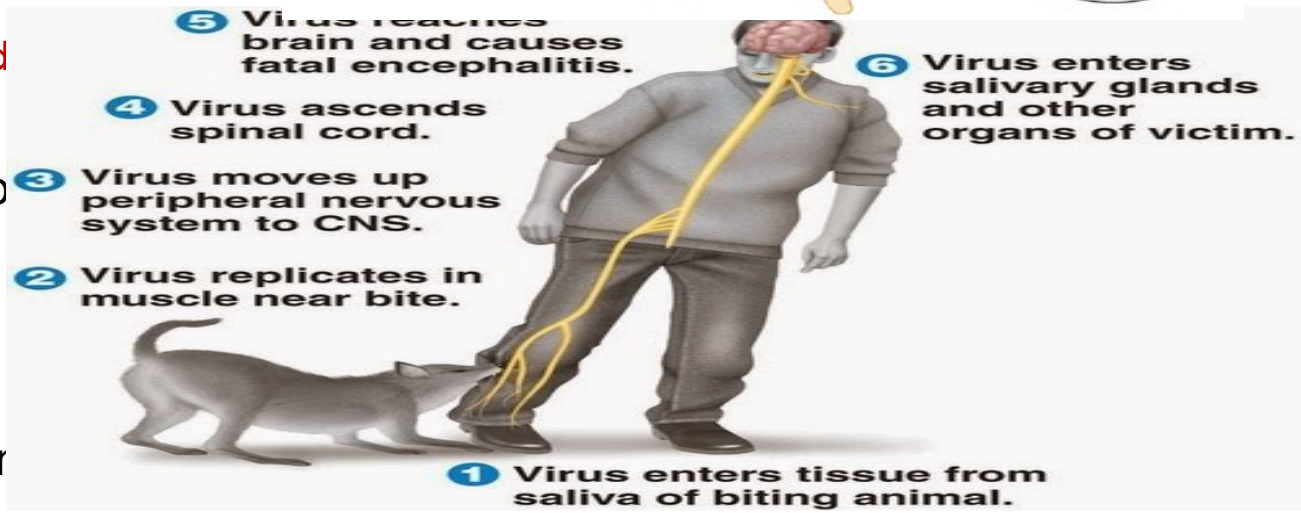
Neuronal death

Intracyto

incl

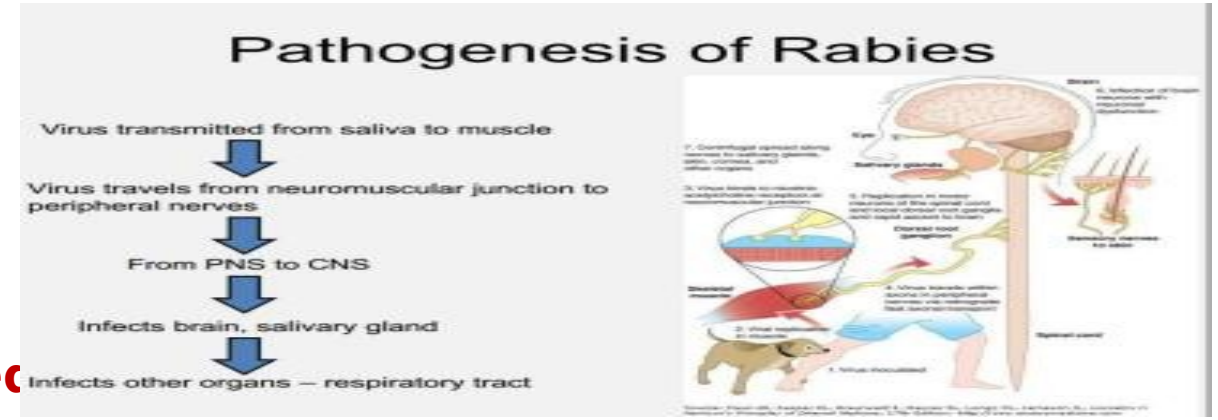
in r




5 brain and causes fatal encephalitis.
6 Virus enters salivary glands and other organs of victim.
4 Virus ascends spinal cord.
3 Virus moves up peripheral nervous system to CNS.
2 Virus replicates in muscle near bite.
1 Virus enters tissue from saliva of biting animal.

Rabies virus

E - Viral spread


Pathogenesis of Rabies
Virus transmitted from saliva to muscle
Virus travels from neuromuscular junction to peripheral nerves
From PNS to CNS
Infects brain, salivary gland
Infects other organs – respiratory tract

1-Virus migrates via peripheral nerves to :

a-Salivary glands → saliva → transmitted

b-Eye , skin & Kidneys

2- Viral replication is restricted to neuronal tissu

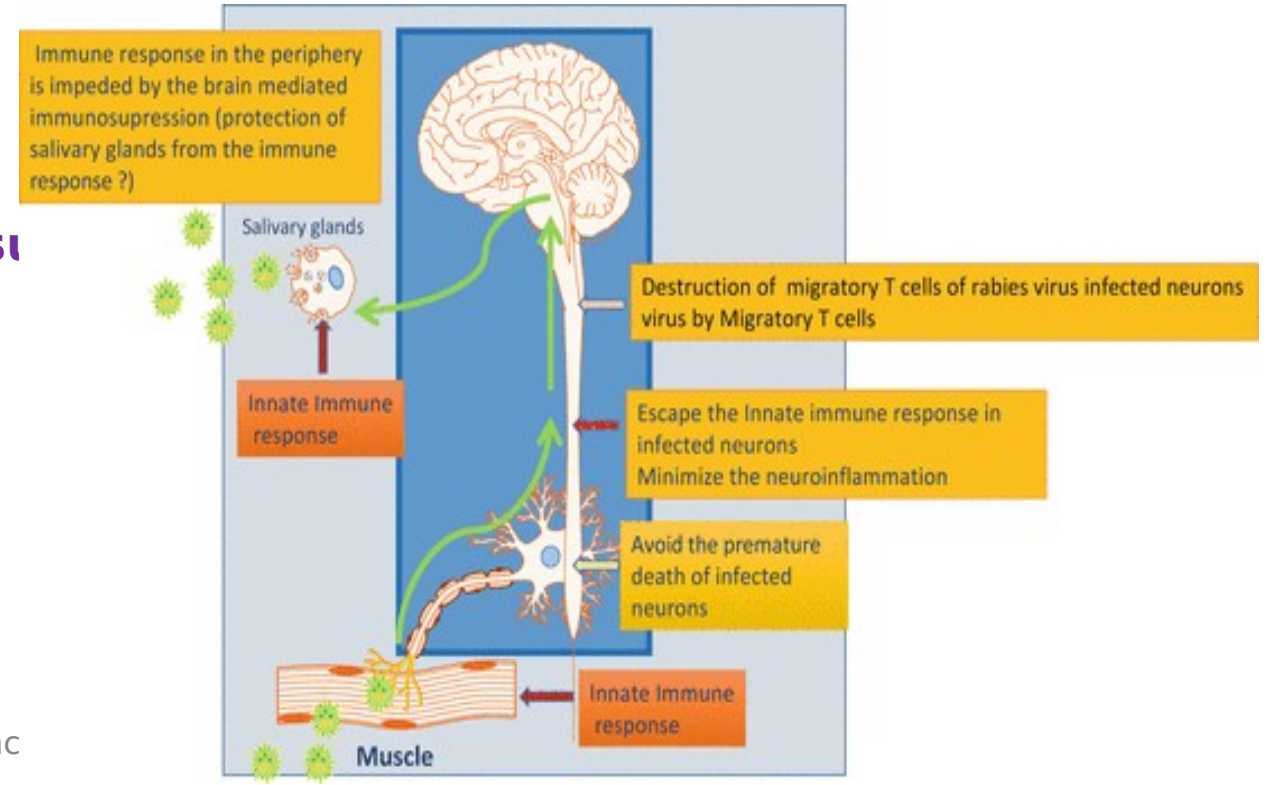
with no viremia

⬇

Virus is **protected** from immune system

⬇

No or little immune response


Immune response in the periphery is impeded by the brain mediated immunosupression (protection of salivary glands from the immune response ?)
Salivary glands
Innate Immune response
Destruction of migratory T cells of rabies virus infected neurons virus by Migratory T cells
Escape the Innate immune response in infected neurons
Minimize the neuroinflammation
Avoid the premature death of infected neurons
Innate Immune response
Muscle

Rabies virus

Clinical manifestations

A-Incubation Period : 2 weeks - 3 months.

- **Shorter in children and with bites in the head and neck** (ma

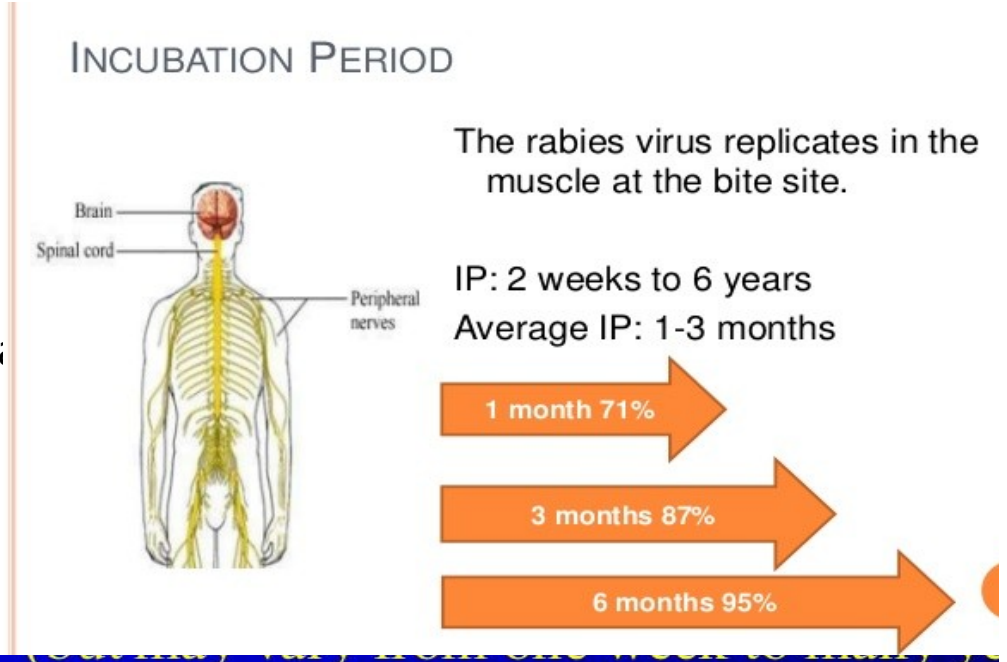
because the virus has a shorter distance to travel

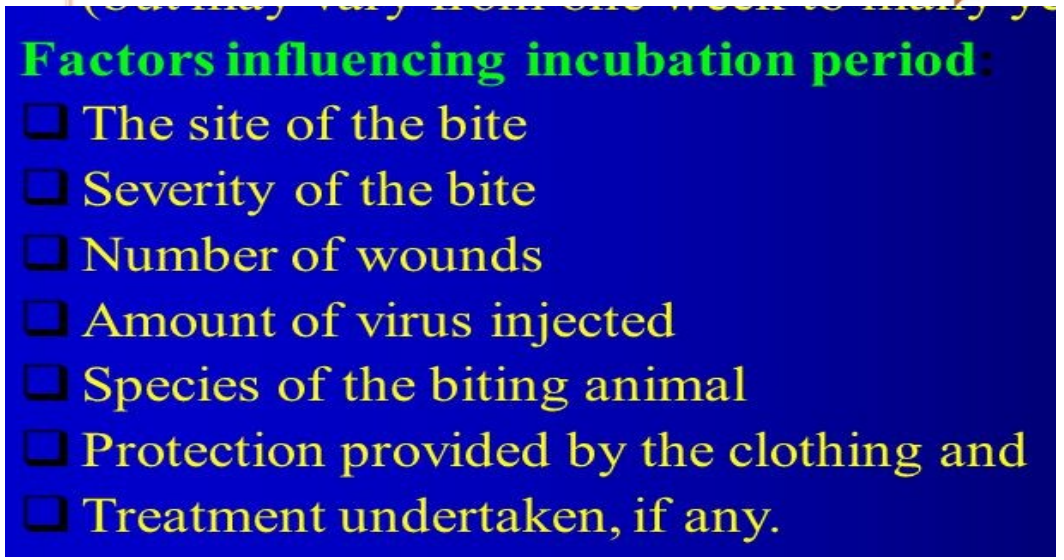
to reach the central nervous system

- **Longer when bites are in the lower limbs**(up to one year)

Long IP allows post-exposure active immunization

to be effective in prevention of the disease.




Factors influencing incubation period:
The site of the bite
Severity of the bite
Number of wounds
Amount of virus injected
Species of the biting animal
Protection provided by the clothing and
Treatment undertaken, if any.

B- Prodromal (non specific) phase: mild fever and pain or paresthesia at the bite site

C-Forms of disease : Rabies manifests

Either

Furious rabies = hyperactivity

(rapidly fatal brain stem encephalitis)

- The person/animal becomes extremely **irritable and aggressive**
- **Hydrophobia** (painful pharyngeal spasms when offered water due to infection of salivary gland)
- **Convulsions.**

Or

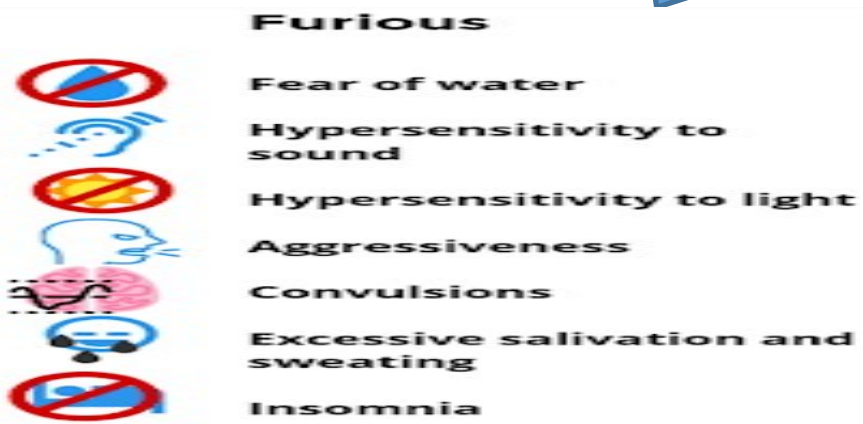
Dumb rabies = paralytic rabies

(spinal cord primarily involved)

- **Ascending flaccid paralysis**

  with pain in the affected muscles
- **Respiratory paralysis.**

Death



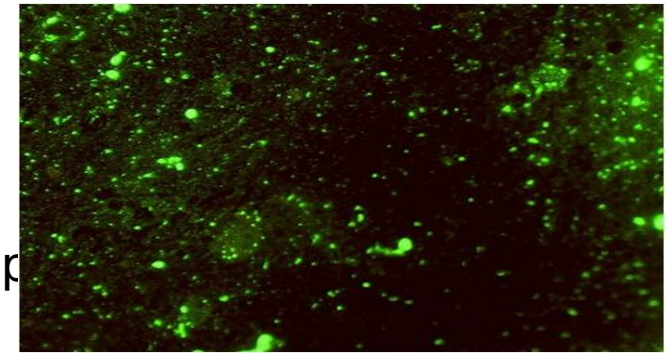
Rabies virus

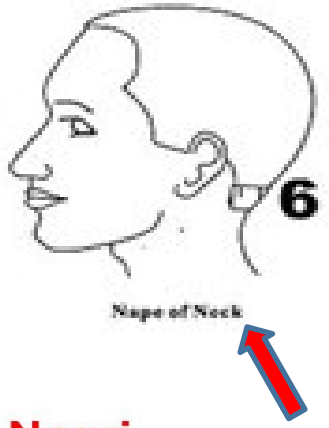
Laboratory diagnosis

A-Direct virus demonstration

1- DIF stain to detect Ag : in a biopsy from the nap

The test of choice in a live patient





2-RT-PCR to detects RNA : in CSF or saliva

B-Isolation of the virus : from saliva, spinal fluid, and b

1- Intracerebral inoculation in mice → **Encepl**

2- On human diploid cell culture

@ Cytology of brain tissue for Negri inclusion bodies in nerve cells.

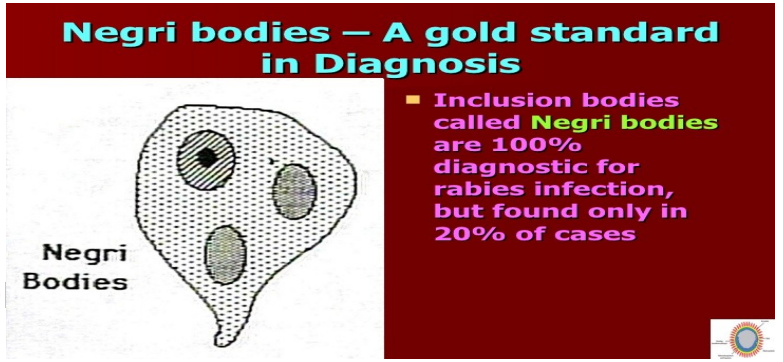
@ Immunofluorescence to detect rabies antigens in the brain

@ Isolation by inoculating mice.

@ Electron microscopy to detect the bullet-shaped virus.

C-Serology :

Serum & CSF Abs appear late during disease progression

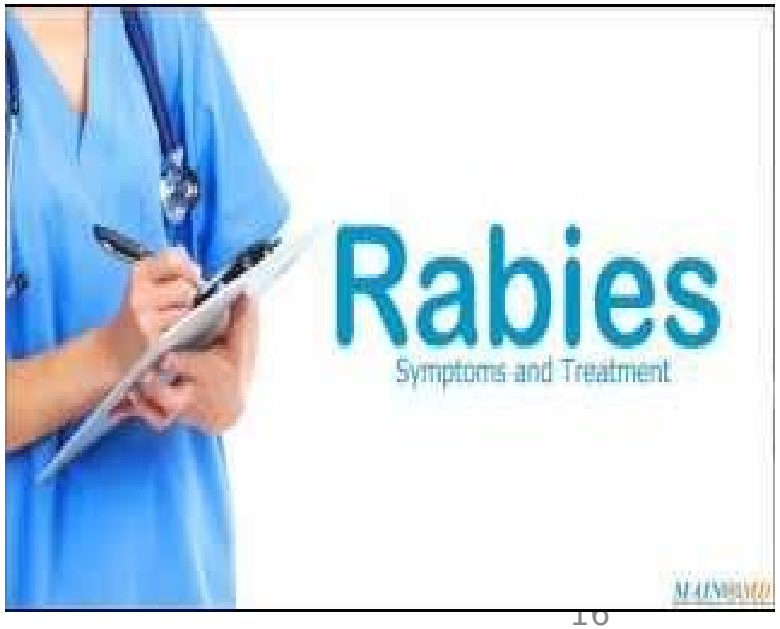

Negri bodies – A gold standard in Diagnosis
Inclusion bodies called Negri bodies are 100% diagnostic for rabies infection, but found only in 20% of cases
Negri Bodies

Post mortum diagnosis

Detection of **Negri bodies in corneal scrapings and in brain o**

Treatment

- After the appearance of the clinical symptoms of rabies, there is ***no effective treatment.***
- Only supportive treatment is available.



Rabies virus

Prevention

A- Post-exposure prophylaxis

Immediate cleaning of the wound with soap & wate

+

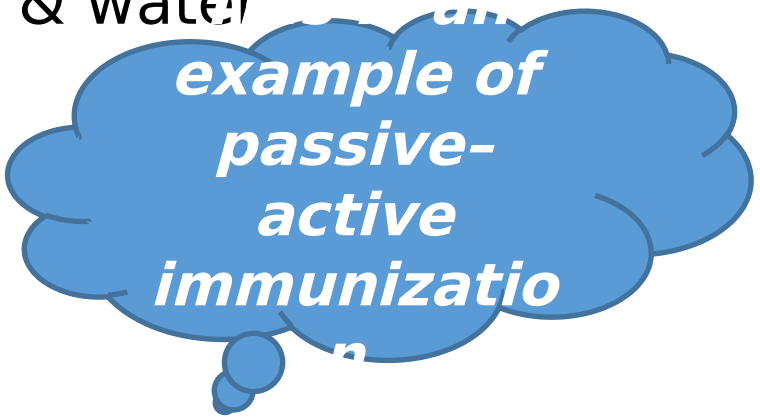
Tetanus prophylaxis.

+

Rabies vaccine (containing inactivated virus)

+

Rabies immune globulin (RIG)



Rabies virus

Human rabies Igs (RIG)

Source

From **hyperimmunized** persons

Administration

As much as possible should be infiltrated

into and around the wound(s)

& any remaining volume should be given

IM site distant from vaccine administration

Recommended prophylaxis in exposed individuals not previously vaccinated against rabies

Wound site(s)	Immediate thorough cleansing of all wounds with soap and water. Tetanus prophylaxis; antibiotics
Human Rabies Immune Globulin (RIG)	20 IU/kg body weight • As much of the RIG as possible should be infiltrated in wound(s) • The remainder should be given IM at a site distant from vaccine
Rabies Vaccine	IM (1 mL) in the deltoid area on days 0, 3, 7, 14, and 28

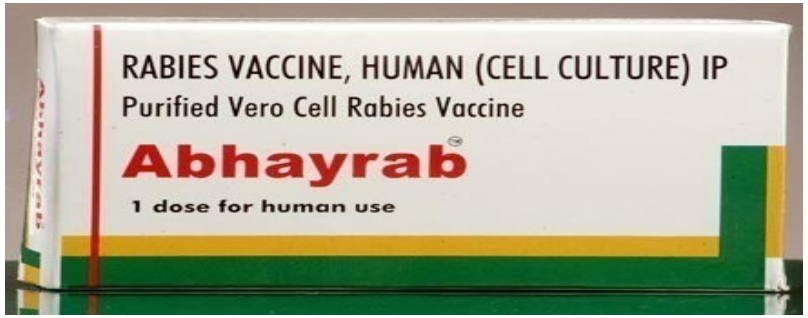
MMWR 48: RR-1, 1999

Rabies virus

Rabies Vaccines

Preparation

Inactivated cell derived vaccines

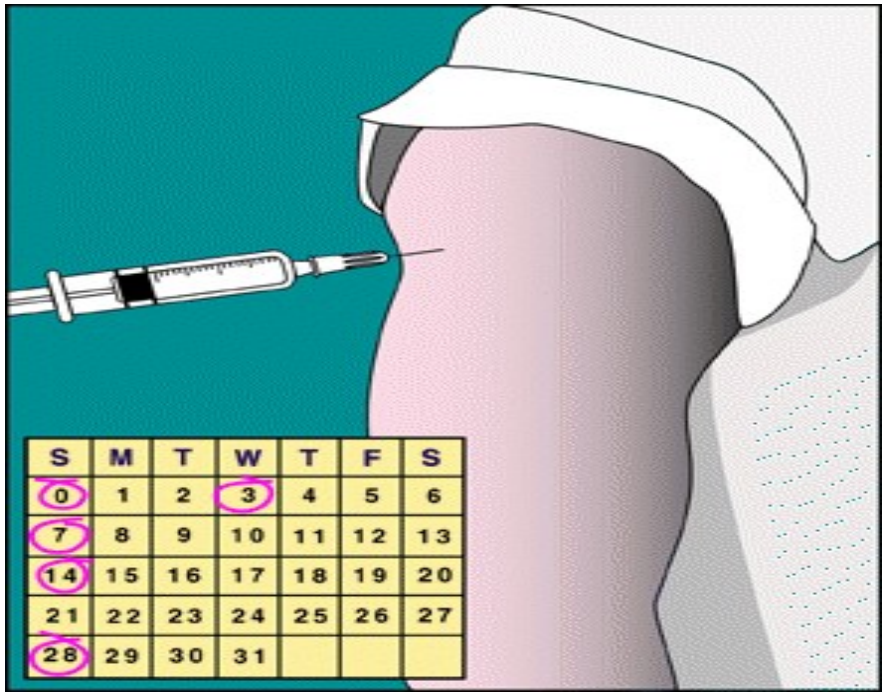


Types

1 - Human diploid cell vaccine (HDCV) : Gold standard

2-Rhesus monkey vaccine

3- Duck embryo vaccine : Low immunogenecity



Dose

-Five IM doses (1 ml. each in deltoid area) **of HDCV ,**

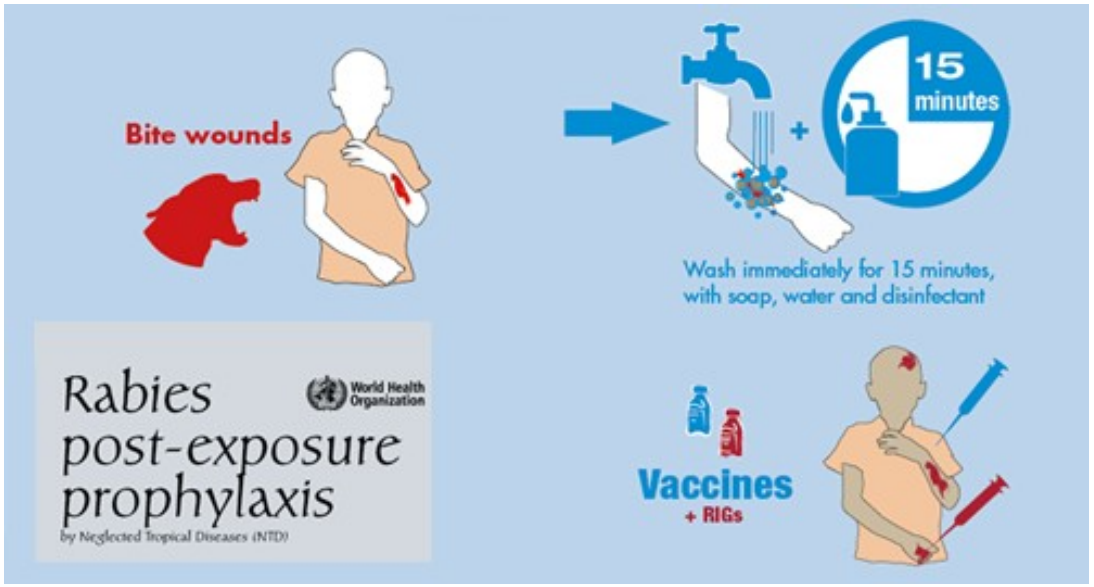
on days 0,3,7,14,and 28.

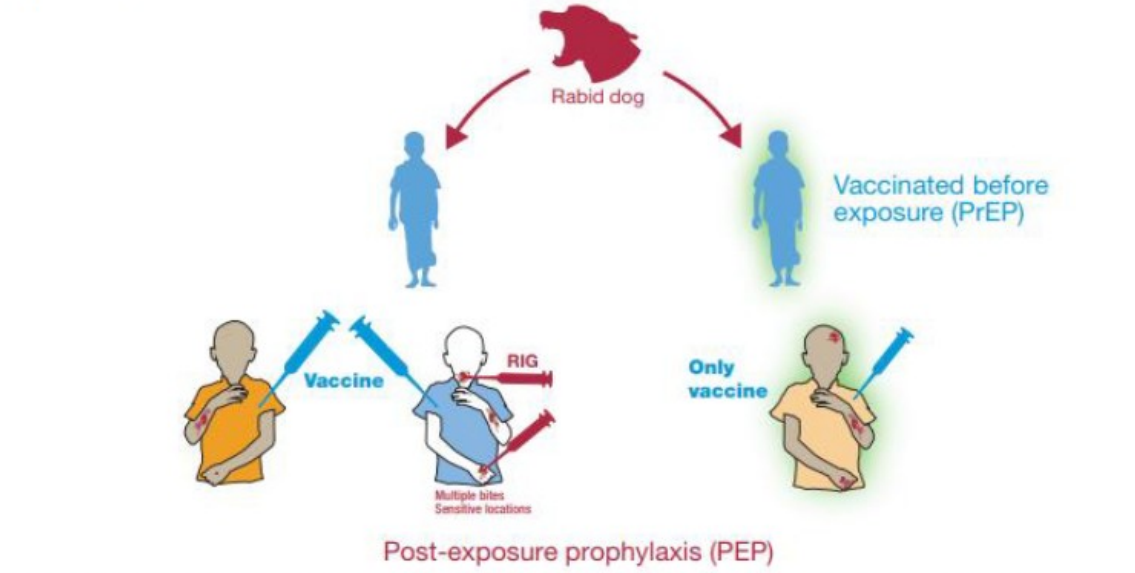
Safe

Pregnancy is NOT a contraindication

Rabies virus

- For previously vaccinated persons should receive **two IM doses (1 mL each) of vaccine, one immediately and one three days later.**
- RIG is unnecessary for previously vaccinated persons are those who have received one of the recommended preexposure or postexposure regimens and had a documented rabies antibody titer.





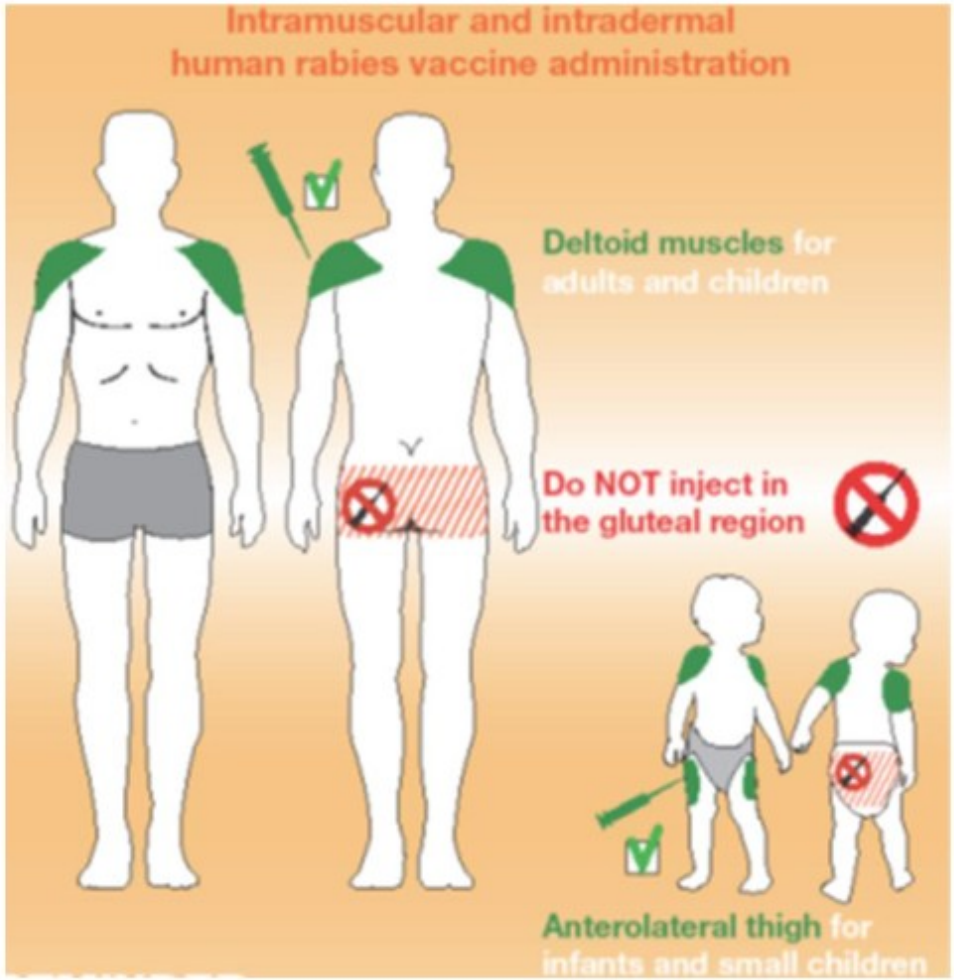

Intramuscular and intradermal human rabies vaccine administration
Deltoid muscles for adults and children
Do NOT inject in the gluteal region
Anterolateral thigh for infants and small children

Figure 3. Sites for intramuscular and intradermal administration of human rabies vaccine (WHO Expert Consultation on Rabies Third Report, 2018)

Rabies virus

Factors affecting the decision to give post-exposure prophylaxis

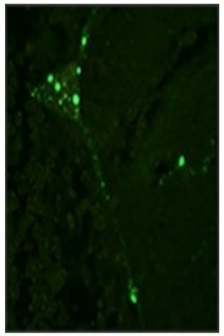
1-The type of animal

a. All attacks from wild animals demand immunization

b. Domestic animals ; whether:

i. the animal was adequatly immunized

ii. The animal is available to be observed



Rabies Diagnosis

Animal diagnosis

- **Post-mortem testing**
- **Direct Fluorescent Antibody (DFA) test**
  - **Antigen of virus in brain tissue**

Discontinue PEP if the animal was captured & proved to be non rabid by DIF

2-Whether rabies is endemic

3-Any one coming into contact with CSF,saliva or mucus membrane

of suspected person should receive complete prophylaxis

(although no documented human to human transmission)

Rabies virus

B-Pre-exposure prophylaxis

1-Indications : few people

a-High risk individuals

i-Veterinary doctors & laboratory workers

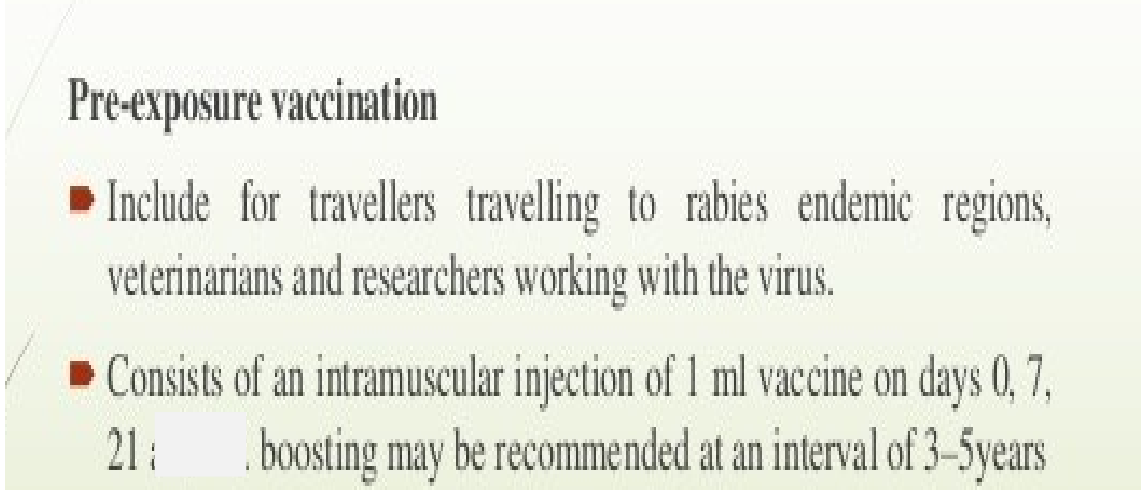
ii-Animal & bat handlers

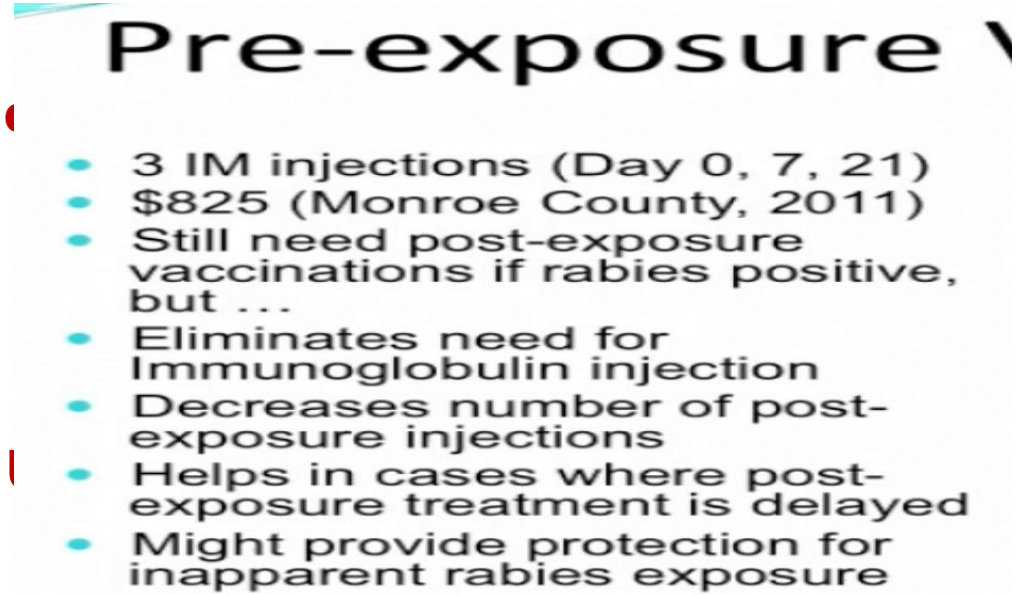
2-Traveler's to countries where rabies is widesprea

2-Doses

3 doses: day **0,7, 21**

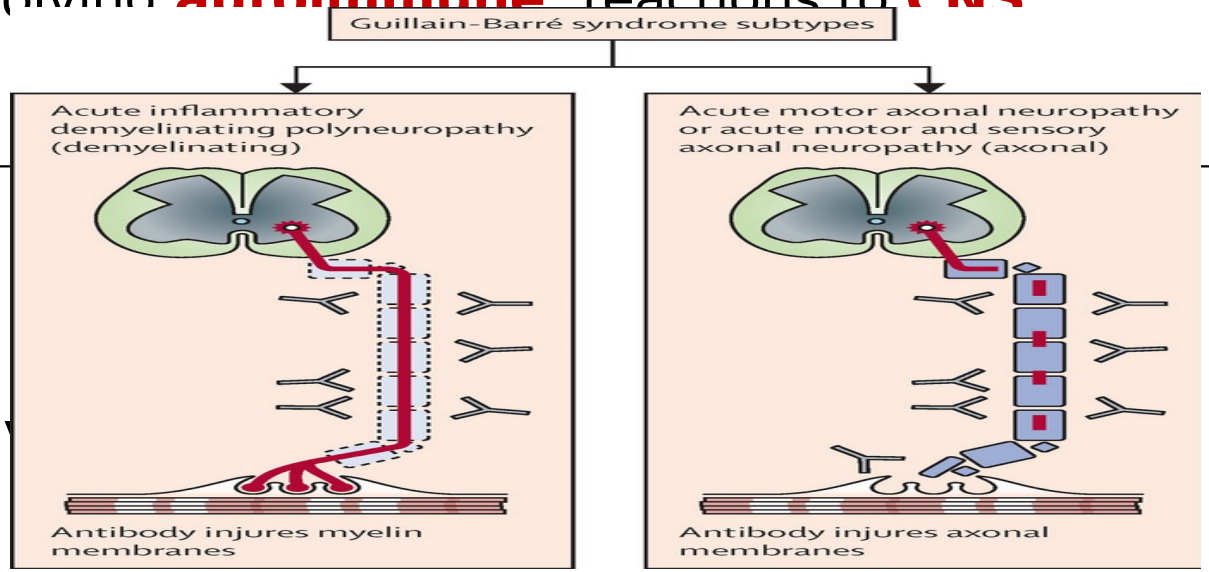
Check rabies Ab titre periodically **(must be >0.5 I**


Pre-exposure vaccination
Include for travellers travelling to rabies endemic regions, veterinarians and researchers working with the virus.
Consists of an intramuscular injection of 1 ml vaccine on days 0, 7, 21 ; . boosting may be recommended at an interval of 3–5years


Pre-exposure
3 IM injections (Day 0, 7, 21)
$825 (Monroe County, 2011)
Still need post-exposure vaccinations if rabies positive, but ...
Eliminates need for Immunoglobulin injection
Decreases number of post-exposure injections
Helps in cases where post-exposure treatment is delayed
Might provide protection for inapparent rabies exposure

Post-Infectious Encephalitis

Definition	Occurs **several weeks** following **infection** **or** **immunization** by some **viruses**
Characters	**Milder form** of encephalitis
Etiology	**Demyelinating disease** involving **autoimmune** reactions to **CNS antigens**
Examples	**1-Guillain-Barré syndrome** Associated with **Human immunodeficieny** **Cytomegalovirus**, and **Epstein-Barr virus**


Guillain-Barré syndrome subtypes
Acute inflammatory demyelinating polyneuropathy (demyelinating)
Antibody injures myelin membranes
Acute motor axonal neuropathy or acute motor and sensory axonal neuropathy (axonal)
Antibody injures axonal membranes

Post-Infectious Encephalitis

Examples

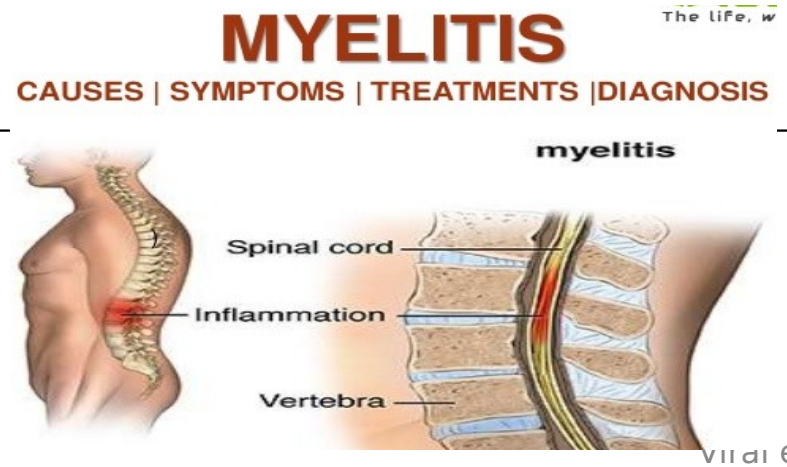
2-Transverse myelitis OR Tropical spastic paraparesis (TSP)

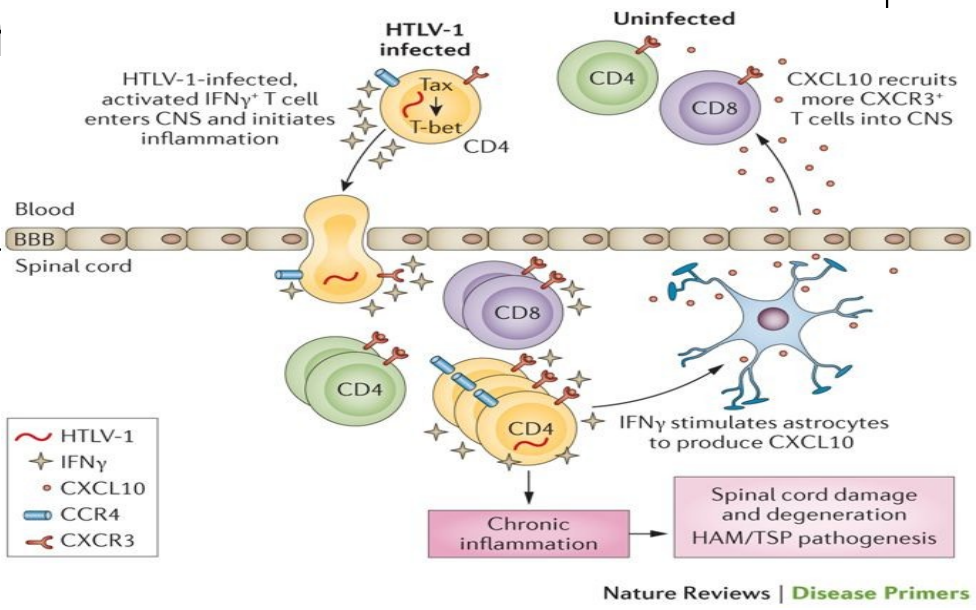
- Associated with **Human T-lymph tropic virus 1(HTLV1)**
- **Slowly progressive demyelinating disease** of the brain & motor neurons in the spinal cord due to either:

a-Autoimmune cross reaction against HTLV-1 that damages neurons

b-Cytotoxic T cells that kill HTLV-infected neurons

c-HTLV-1 Infected T helper cells induce in





Quiz

A woman was wandering in a park, when a cat appeared and bit her on the leg! She now presents to your emergency room about an hour after the bite. Which one of the following is the most appropriate thing to do?

a) Test the patient's serum for rising antibody titer before treating her.
b) Reassure her that rabies is not a problem because cats do not carry rabies.
c) Quarantine the animal for 10 days and only treat her if signs of rabies appear in the animal.

Quiz

A 25 years old female patient presents to the emergency room disoriented and confused. She was unable to remember where she lived or even her phone number. She begins to hallucinate and salivate excessively. She expressed a marked phobia when the water tap was opened.

What is the most likely causative agent

Suggested Textbooks

1. Levinson’s Review of Medical Microbiology
   from page 639:640
   from page 1307:1311